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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/216,609	12/21/1998	HANS JOHN HANSEN	018733/0734	9388

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EXAMINER

YAEN, CHRISTOPHER H

ART UNIT PAPER NUMBER

1642

DATE MAILED: 03/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/216,609

Applicant(s)

HANSEN, HANS JOHN

Examiner

Christopher H Yaen

Art Unit

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 December 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-53 is/are pending in the application.
- 4a) Of the above claim(s) 8-13, 15-22, 27, 28, 34-35, 42-44, 47 and 48 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 23-26, 29 and 30 is/are allowed.
- 6) ☒ Claim(s) 1-7, 14, 31-33, 36-41, 45-46, 49, 50-53 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

1. The examiner of the application has changed. This case has now been transferred as of January 8, 2002. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Christopher Yaen, Group Art Unit 1642.
2. Applicants amendment filed December 31, 2001 is acknowledged, and accordingly, claims 1, 33, and 40 have been amended. Claims 1-7, 14, 23, 24, 25, 26, 29, 30, 31, 32, 33, 36, 37, 38, 39, 40, 41, 45, 46, 49, 50-53 are being examined in the merits.

Response to Arguments

Claim Rejections - 35 USC § 112 Withdrawn

3. The rejection of claims 23-27, 29, 30, and 33 rejected under, 35 USC§112 second paragraph, is **withdrawn** in light of the amended claim language of claim 1.
4. The rejection of claims 40 and 41 under, 35 USC§112 second paragraph, is **withdrawn** in light of the amended claim language of claim 33.

Election of Species/Cancellation of Claims

5. Applicant traverses the withdrawal of claims 30, 33-35, and 44, stating that the claims are directed to the elected species of enzyme: carboxylesterase; prodrug: CPT-11; target site:CEA antigen; therapeutic agent: camtothecin. Upon

further consideration, claims 30 and 33 will be rejoined, and will be examined on the merits. Applicant's arguments are considered and are found not persuasive for claims 34-35 and 44. Claim 34-35 and 44 are further limitations of claims 33 and 1, but are drawn to other groups of non-elected species for the therapeutic agents (radionucleotides (I-131, I-125, At-211), α/β -emitting radioisotopes drugs, toxins, boron addends, vasodilator, cytokine, photosensitizer, or radiosensitizer). Thus, these claims are not drawn to elected species and will not be considered.

Priority

6. Upon further review, the consideration for priority on claims 1-6, 11, 16-18, 20, 31-34, 36, 39, 42-44, 46, and 49-52 will **not** be accorded the earlier filing date of April 18, 1988. US Patent Application No. 07/182623, now abandoned (grandparent) and US Patent Application No. 08/445,110 (parent), now US Patent No. 5,851,527, do not disclose of a *"multispecific targeting protein"* or *"targeting protein-enzyme conjugate"* as to enable an artisan to make and use the product claimed in the instant application. Firstly, applicant argues that the (grand)parent application discloses that monoclonal antibodies can be made by *"more unconventional methods such as interspecies fusions and genetic engineering manipulations of hypervariable regions"* and that a skilled artisan would be able to readily make a single chained antibody or binding moieties. Applicants arguments are not persuasive because, the specification, to which is referred, does not distinctly point out that single chain antibodies are included in

this "*genetic engineering manipulation of the hypervariable region*". This type of engineering refers only to hypervariable regions and not to single chain antibody fusions.

Secondly, applicant argues that the disclosure of fusion proteins can be found on page 8, line 21 through page 9 line 14 of the (grand)parent specification, and states that the disclosure teaches of fusion proteins comprising a targeting protein and an enzyme. Applicants arguments are not persuasive because, the (grand)parent cases do not distinctly disclose of fusion proteins to be made or constructed from proteins other than antibodies. Although antibodies are proteins, the specification does not detail or contemplate the use of other proteins in fusion. The (grand)/parent distinctly point out the use of bi-specific antibodies or antibody–enzyme conjugates.

It is believed that the applicant was in possession of a bi-specific antibody or an antibody-enzyme fusion, but it is believed that the applicant has not meet the written description requirement for any "*multispecific targeting protein*" or "*targeting protein-enzyme conjugate*".

US Patent Application No. 07/182623 and US Patent Application No. 08/445,110 disclose of an antibody-enzyme conjugate or a bispecific antibody (pg 8-9 of specification), but makes no mention of any "*multispecific targeting protein*." The instant application broadens the scope of the previously claimed inventions, and hence does not describe the full scope of the instant application.

Therefore, the instant application is not accorded the earlier filing date of April 18, 1988.

Claim Rejections - 35 USC § 103 Maintained

7. The rejections of claims 1, 2, 5, 7, 14, 45, 46, and 49-52 rejected under, 35 USC§103(a) as being obvious over Iwasa *et al.* in view of Bosslet *et al.* or Blakey *et al.* and further in view of Potter *et al.*; claims 1-7, 14, 45, 46, and 49-52 rejected under, 35 USC§103(a) as being obvious over Iwasa *et al.*, in view of Bosslet *et al.* or Blakey *et al.* and further in view of Potter *et al.*, and further in view of King *et al.*; claims 1,2,5-7, 14, 36-41, 45, 49-52 rejected under, 35 USC§103(a) as being obvious over Iwasa *et al.* in view of Bosslet *et al.* or Blakey *et al.* further in view of Potter *et al.* and further in view of Griffiths *et al.* ; claims 1, 31, and 32 rejected under, 35 USC§103(a) as being obvious over Iwasa *et al.* in view of Bosslet *et al.* or Blakey *et al.*, further in view of Potter *et al.* and further in view of Sharma *et al.*; and claim 53 rejected under, 35 USC§103(a) as being obvious over Bosslet *et al.* or Blakey *et al.* in view of Potter *et al.* are **maintained**.

Applicant argues that claims 1,2,5,6,46, and 49-52 should be accorded the earlier filing date of April 18, 1988, and antedates the references that are used in the, 35 USC §103(a) rejection. The arguments set forth by the applicant are not persuasive for the reasons stated above (see **Priority**). For claims 7, 12, and 45, applicant argues that the references do not teach or suggest all of the claimed elements of the instant application, do not motivate to combine these references

to conceive of the inventions of the instant application, and do not provide a reasonable expectation of success at arriving at the instant invention. Applicant's arguments are considered and are not found persuasive for the following reasons.

Firstly, applicant states that the Iwasa *et al.* reference does not teach of using a proagent-activating enzyme as part of the bi-specific antibody that has “(1) specificity for a determinant of a target, (2) a second specificity for an enzyme to convert a proagent to an active agent at the target site”. Iwasa *et al.*; however, does teach of a hybrid antibody or bi-specific antibody that has its actual determinant for fibrin and thrombolytic substances, hence a specificity of a determinant. Furthermore, Iwasa *et al.* also teach of using proagent-enzymes as part of their bi-specific antibody, by the contemplation of using TPA or Tissue Plasminogen Activator (column 4, lines 6-15), an enzyme that catalyzes the conversion of plasminogen to plasmin. Applicant also contends that the invention claimed by Iwasa *et al.* does not overcome the problem of minimizing cytotoxicity to non-targeted cells. Although Iwasa *et al.* do not specifically teach of using pro-drugs that can be activated by their respective enzymes, Iwasa *et al.* already contemplated using an enzyme that is capable of converting pro-proteins to proteins, hence it would have been obvious to one of ordinary skill to contemplate the use of a pro-protein or pro-drug that could be activated by an enzyme that converted the pro-protein or pro-drug to its active form and hence minimize the cytotoxicity of a protein or drug. In addition, applicant argues that

the invention presented by Iwasa *et al.* indicates a drawback and states that the enzyme used by Iwasa *et al.* is to be used as a therapeutic agent itself. Iwasa *et al.*, however, states that the enzyme can be "*a substance which promotes*" (column 4, line 8).

Secondly, applicant argues that the use of the secondary references (Bosslet, Blakey or Potter *et al.*) in combination with the Iwasa *et al.* reference do not set forth any motivation to combine and conceive of the instant application. For the reason set forth above and the reason already stated on the record (previous office actions) regarding the secondary references, the arguments presented by the applicant is not found persuasive.

Thirdly, in regards to the other claim rejections, (1-7, 14, 45, 46, and 49-52 obvious over Iwasa *et al.* in view of Bosslet *et al.* or Blakey *et al.* and further in view of Potter and further in view of King *et al.*; 1,2,5-7,14,36-41,45,46, and 49-52 obvious over Iwasa *et al.* In view of Bosslet *et al.* or Blakey *et al.* and further in view of Potter *et al.* and further in view of Griffiths *et al.*; 1, 31, and 32 obvious over Iwasa *et al.* in view of Bosslet *et al.* or Blakey *et al.* and further in view of Potter *et al.* or Sharma *et al.*; and 53 obvious over Bosslet *et al.* or Blakey *et al.*) applicant argues that the reliance of rejection on Iwasa *et al.* is improper and the combination with the secondary references do not substantiate the deficiencies that exist in Iwasa *et al.* Applicant's argument is noted and is not persuasive for the same reasons set forth above. Therefore, the claims set forth in the instant application are obvious.

Lastly, because the priority date used in the examination of the instant application is December 21, 1998, all of the above references antedate the claims of the instant application.

Double Patenting Maintained

8. The rejection of claims 1-6, 11, 12, 16-18, 20, 31-34, 36, 39, 42-4, 46, 49-53 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of US Patent 5,851,527 is maintained for the reasons of record. Applicant states that a terminal disclaimer will be provided upon allowance of claims. Until applicant provides a proper terminal disclaimer, said rejections is maintained.

Conclusion

9. Claims 1-7, 14, 31-33, 36-39, 40, 41, 44-46, 49-53 are rejected. Claims 23, 24, 25, 26, 29, and 30 are free of prior art.
10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will


Art Unit: 1642

the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
March 7, 2002


ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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